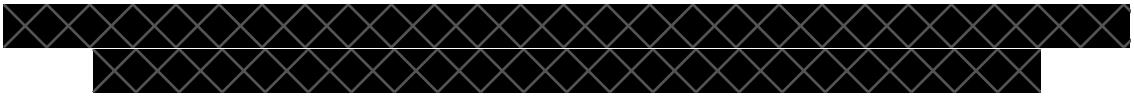
CLINICAL INVESTIGATION PLAN (CIP)

EN ISO 14155

Klinischer Prüfplan (MPG §3)

Clinical Outcome of Electrical Auricular Vagal Stimulation in Patients with Stable Symptomatic Chronic Heart Failure -a Pilot Study



[1]*Dept. Of Special Anaesthesia and Pain Therapy, Medical University Vienna*
[2]*Dept. Of Internal Medicine II, Medical University Vienna*
[3]*CeMSIIS, Medical University Vienna*

Version 1.0 / Date 03.12.2012

Confidentiality Statement
The information contained in this document, especially unpublished data, is the property of the sponsor of this clinical investigation Dept. Of Special Anaesthesia and Pain Therapy, Medical University Vienna. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Independent Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the Dept. Of Special Anaesthesia and Pain Therapy, except to the extent necessary to obtain informed consent from those persons to whom the interventional devices may be administered.

Device Name and Manufacturer	P-STIM®
CIP authors	[redacted]
Academic investigators	[redacted]
Document type	Medical Device CIP
Document status	
Date	03.12.2012
Number of pages	30

1. SPONSOR, INVESTIGATOR, MONITOR AND SIGNATURES

Clinical investigator (MPG § 3)

[redacted] *Dept. of Special Anaesthesia and Pain Therapy, Medical University Vienna*

_____ _____
Signature Date

[redacted] *Dept. of Internal Medicine II, Medical University Vienna*

_____
Signature Date

Sponsor/OEL (MPG § 3)

[redacted] *Dept. of Special Anaesthesia and Pain Therapy, Medical University Vienna*

_____ _____
Signature Date

Representative of CRO (EN ISO 14155)

Name:

_____ _____
Signature Date

Statistician

Name: [redacted]

_____ _____
Signature Date

2. SYNOPSIS OF THE CLINICAL INVESTIGATION

TITLE	**Clinical Outcome of Electrical Auricular Vagal Stimulation in Patients with Stable Symptomatic Chronic Heart Failure -a Pilot Study**					
ACRONYM	(abbreviated title)					
NAME OF DEVICE	*Dev1*					
DESCRIPTION OF THE PROCEDURES	P-Stim® is an investigational device intended to deliver electrical auricular acupuncture in individuals suffering from heart failure. The device system is to be used only in accordance with the approved Investigational Plan on subjects who have signed an informed consent form. Device use is limited to the approved study investigators.					
OBJECTIVES	In this study the effects of electrical auricular acupuncture on symptomatic chronic heart failure will be assessed. **Primary Objective**: - Six-minute walk test **Secondary Objective:** - Left ventricular ejection fraction (LVEF) - New York Heart Association (NYHA) classification - In addition the patient's quality of life (regarding to different areas in daily life, mobility etc.) will be assessed by a quality of life questionnaire (SF 36) - Adverse events of acupuncture will be recorded - Inflammatory cytokines TNF α, IL6, NT-proBNP, CRP, will be collected to measure a possible influence of electrical auricular acupuncture on inflammation - Ventricular and/or atrial arrhythmia documented in a subgroup of patients with implanted cardiac rhythm management devices.					
TYPE OF THE INVESTIGATION	Prospective, single center, randomized, parallel group, double-blind, placebo-controlled					
PERIOD OF ENROLMENT	**First patient First visit**	*1.1.2013*	**Last patient First visit**	*31.12.2013*	**Last patient Last visit**	*28.2.2014*
CENTER(S) / COUNTRY(IES)	*1 center, Medical University Vienna, Austria*					
PATIENTS / GROUPS	*40* patients in *2* groups *20* patients *per* group *Randomization ratio 1:1, stratification gender*					
INCLUSION CRITERIA	- Stable symptomatic chronic heart failure, defined by: - NYHA Classification II-III - Optimal medical treatment (ESC guidelines 2012) for at least 1 month					

	- LVEF <40% - Patients must be able to understand study conditions - No exclusion criteria - Signed informed consent
EXCLUSION CRITERIA	- Ventricular tachyarrhythmia within 1 month prior to base line visit - Any electrical auricular vagal stimulation treatment within 6 months prior to base line visit - Participation in another clinical trial within 3 months prior to base line visit - Psoriasis vulgaris - Hemophilia - Cardiac pace makers
COMPARATIVE DEVICE	Placebo
CONCOMITANT MEDICATION/CON-COMITANT DEVICE	**Not applicable**
EFFICACY ENDPOINTS	Clinical outcome of heart failure definition see above
TOLERABILITY / SAFETY ENDPOINTS	Adverse Events will be recorded
QUALITY OF LIFE	SF 36 questionnaire
STATISTICAL METHODOLOGY	• **Primary Endpoint** 6 minute walk test • **Null and alternative hypotheses:** ***H_0*** *electrical auricular vagal stimulation does not increase 6min walk test* ***H_1****: electrical auricular vagal stimulationt increases 6min walk test* **Type-I and -II errors - power.** *α 0.05 (two sided)* *ß 0.20 (Power =80%)* **Interim analysis** . • **Statistical methodology** The primary end point (walking distance in 6 minutes) will be analysed by analysis of covariance, taking the baseline value as covariate into account, and the treatment group as factor. Continuous secondary outcome variables will be analysed by analysis of covariance as described above. Change in NYHA classification will be described by contingency tables, and the percentage of patients with an improvement in NYHA will be compared using a Fisher's exact test. • **Sample size calculation.** We assume a clinically relevant difference in the improvement in walking distance of 30 meters comparing the electrically stimulated

	acupuncture group to the Placebo group. Furthermore, we assume a standard deviation in the improvement o the walking distance of 30 meters (Kristen 2010). A sample size of 17 in each group will have 80% power to detect this clinically relevant difference between the groups using a two group t-test with a 0,050 two-sided significance level. Because of the possibility of drop-outs we include 2x20 patients. • **Main analysis set:** *Intention to treat* • **Other endpoints**
STUDY EXTENSION	.

3. CONTENTS

4. INTRODUCTION

4.1 Background information

a) Nerve Supply of the auricle

Peuker at al found a heterogenous distribution of cranial branchial nerves and somatic cervical nerves in the auricle [1]. The lateral surface of the auricle is innervated by the great auricular nerve (GAN), the auricular branch of vagus nerve (ABVN) and the auriculotemporal nerve (ATN). Peuker et al also provided an overview of the innervations pattern of the lateral surface of the auricle. ABNV mainly supplies the cymba conchae (100%), cavity of concha (45%), the tragus (45%) and the Antihelix (73%) [1]. Some parts of the lateral surface of the auricle show a double innervation.

b) Vagal stimulation in heart failure

Heart failure is characterized by an autonomic imbalance with withdrawal of vagal activity and increased sympathetic activity [2]. This autonomic imbalance can be quantified by the BRS (Baroreflex sensitivity) or by heart rate variability. Lower BRS is related to a higher mortality in heart failure [3], [4].
During acute myocardial ischemia (when the heart dilates) vagal and sympathetic afferent fibers increase their firing [2]. At the ventricular level, sympathetic fibers are dominant, which leads to a sympathetic excitation and to the cardio-cardiac sympathetic reflex [2].
This afferent sympathetic activity inhibits the cardiac vagal efferent activity.

c) The role of inflammatory cytokines in heart failure

Until a few years ago heart failure (HF) was considered a hemodynamic disorder. Recent studies however clearly show a correlation of HF to neurohormones. Several trials suggest an increased expression of TNFα, IL-6, IL-18, cardiotrophin-1 and Fas ligand as well as other chemokines in patients with HF [5], [6], [7],[8]. Some of these elevated neurohormones are also associated with a deterioration of LVEF (left ventricular ejection fraction) or NYHA Classification [7],[6],[9]. Inflammation also plays a role in post-myocardial infarction remodelling. During the acute phase of myocardial infarction cytokines are an intrinsic response to the injury in the myocardium. The cytokines mainly involved in this process of wound repair, scar formation and compensatory hypertrophy are TNFα, IL-6 and IL-1β [10], [11]. While a moderate inflammatory response induces a survival activating factor enhancement pathway [12], a persistent inflammatory response may lead to heart failure [13].
For risk stratification and evaluation of therapeutic responses in heart failure, mainly NT-proBNP (natriuretic peptide) is used as biomarker. NT-proBNP also guides therapy in heart failure [14]. In addition CRP (C-reactive protein) gained a leading role as an inflammatory biomarker in cardiovascular disease mainly because of its ability to reflect upstream inflammatory activity. A large clinical trial associated increased CRP levels with features of more severe HF and adverse clinical outcome [15].
Although NT-proBNP is a strong biomarker in HF, it is unlikely that it reflects all the pathogenic processes involved in this complex disorder [11]. Therefore the role of other inflammatory cytokines in HF has to be investigated.

5.2. Rationale of the clinical investigation

Chronic heart failure is one of the most serious medical problems in industrial countries. Despite optimized heart failure therapy the prognosis remains bad. Raised inflammatory cytokines are causing skeletal muscle fatigue and activation of muscle ergoreceptors, subsequently leading to an

increase in ventilation, sensation of breathlessness, perception of fatigue and autonomic dysbalance [16];[17]. Novel approaches to heart failure therapy include selective electrical vagal stimulation to normalize autonomic balance [18]. Vagal Stimulation however remains an invasive technique, which is restricted to therapy-resistant patients. Acupuncture has been shown to act pro-vagotonic [19] and anti-inflammatory [20]. In addition Kristen et al recently showed an improvement of exercise tolerance in patients with HF after acupuncture treatment [17]. A dense vagal innervation of the auricle especially of the triangular fossa and concha has been suggested by Peuker et al [1]. La Marca R et al found an increased vagal activity after electrical acupuncture on the concha of the ear [21].
Electrical auricular vagal stimulation is a totally new approach to therapy in heart failure. It might be a safe complementary treatment in patients with chronic heart failure. As there are no clinical studies on this topic its effects on heart failure have to be further investigated.

5. OBJECTIVES OF THE CLINICAL INVESTIGATION (HYPOTHESIS)

5.1 Primary Objectives (Hypothesis)

In this study the effect of electrical auricular vagal stimulation on chronic heart failure will be assessed. Because of previous studies (Kristen et al.) we chose the following parameter as primary objective:
-6 min walk test

5.2 Secondary Objectives (Hypothesis)

-Quality of Life assessed by SF 36
-adverse events of electrical auricular vagal stimulation will be recorded
-blood levels of inflammatory cytokines TNF α, IL6, NT-proBNP, CRP
-LVEF (assessed by transthoracal echocardiography)
-NYHA (New York Heart Association) classification

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1 Population

6.1.1 Subject population

40 patients with chronic heart failure aged from 18-85 will participate in this prospective, double-blind, randomised, placebo-controlled trial.

6.1.2 Inclusion criteria

- Chronic heart failure
- NYHA Classification II-III
- Stable medication since at least 1 months
- LVEF <40%
- Patients must be able to understand study conditions
- No exclusion criteria
- Signed informed consent

6.1.3 Exclusion criteria

- Any electrical auricular vagal stimulation treatment within 6 months prior to base line visit
- Participation in another clinical trial within 3 months prior to base line visit
- Ventricular tachyarrhythmia within 1 month prior to base line visit
- Psoriasis vulgaris
- Hemophilia
- Cardiac pace makers

6.1.4 Duration of the clinical investigation

Patients will stay in the study for 9 weeks consisting of 5 weeks treatment period and 4 weeks follow up period.

6.1.5 Withdrawal and replacement of subjects

Criteria for withdrawal

Subjects may prematurely discontinue from the clinical investigation at any time. Premature discontinuation from the study is to be understood when the subject did not undergo EOS

examination and / or all pivotal assessments during the clinical investigation, i.e. three complete dosage-time profiles.

Subjects must be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the clinical investigation personal

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained.

Follow-up of patients withdrawn from the clinical investigation

In case of premature discontinuation after treatment with the medical device , the investigations scheduled for the EOS visit will be performed 7 days after discontinuation. The subjects will be advised that participation in these investigations is voluntary. Furthermore, they may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected in the course of the clinical investigation will be destroyed.

6.1.6 Premature termination of the clinical investigation

The sponsor has the right to close this clinical investigation at any time. The IEC and the competent regulatory authority must be informed.
The clinical investigation or single dose steps will be terminated prematurely in the following cases:

- If adverse event/adverse devise effect occur which are so serious that the risk-benefit ratio is not acceptable
- If the number of dropouts is so high that proper completion of the clinical investigation cannot realistically be expected.

7. METHODOLOGY

After signing the informed consent patients will be randomized in the verum group (VA) or the placebo group (PA). Patients in the VA group will receive the P-STIM

7.1 Treatment duration and modification

7.2 Medical Device

7.2.1 Medical device and it´s characteristics:

P-STIM is a battery-operated micro-stimulation appliance weighing 5 grams designed as a disposable product for a single use. P-STIM is placed behind the patient's ear and connected to stimulation needles on the auricle. P-STIM offers regular therapy over several days. The appliance transmits low-frequency electric pulses to exposed nerve endings, which triggers the release of endorphins.
The built-in microchip creates periods of stimulation and rest, each lasting approximately 3 hours. After a time it could feel as if the intensity of stimulation is decreasing. A decrease in the perceived intensity of stimulation may be subjective and have no bearing on the effectiveness of the therapy.

7.2.2 Manufacturer (Model or Type Number including software and accessories):

Manufacturer:
Firma Biegler Medizinelektronik
Biegler GmbH
Allhangstrasse 18a,
3001 Mauerbach, AUSTRIA

Appliance: Point stimulation appliance
Type description: P-STIM
Power supply: 3 x 1.4V batteries (Type AC 10E)
Output: (Load impedance range 1k-10k□) max. 3.8V,
Impulse interval 1000ms, Impulse width 1ms, (1Hz / 1ms / bipolar), max possible total duration of treatment 4 x 24 hours
The amplitude of the output signal diminishes in proportion to battery voltage.
Protection level: IP20 | Type: B
Classification (in accordance with Directive 93/42 EEC): II a
Duty type: approx. 3h duty / 3h at rest (periodic duty)
Weight incl. battery: 5 g | Dimensions: 63 x 28 x 8 mm
Needle Dimensions: 0.4 mm width x 2 mm length

7.2.3 Installation and handling instructions

The appliance is splash-proof but not watertight. If desired, hair should be washed before therapy. When showering, the appliance must not be allowed to come into direct contact with water.
Do not use P-STIM and accessories when package is damaged.
The sterile stimulation needles are only intended for SINGLE use.
Do not resterilise!
The re-use of single-use products represents a possible risk of infection for the patient or user. Any product contamination can damage the health of the patient and lead to illness or death.
The Multi-Point stylus, the ring applicator and the stimulation needles are to be used with the P-STIM only and for no other purpose. If a needle is fitted more than three times with the same cap, or the cap is damaged mechanically or the red release button on the Multi-Point is pressed too early, the needle may become detached prematurely. Never hold the Multi-Point against the face or eyes with a needle attached. If the appliance and/or needles become detached, they must not be

refastened by the patient under any circumstances. The patient should visit his doctor as soon as possible in order to have the puncture points disinfected.
When removing the appliance it is important that care be taken to avoid contact with the needles. The needles can be seperated from the P-STIM appliance by carefully cutting through the connection leads. It is important that all contaminated tips or sharp objects in medical use are handled with extreme care (Information taken from P-STIM® User Manual).

Premature permanent discontinuation due to an adverse event

If the reason for premature permanent discontinuation of clinical investigation is an AE, the patient should have a "Premature EOS" visit with all the assessments performed before the discontinuation of the treatment with the medical device, whenever possible.

Premature permanent discontinuation due to another reason than adverse event

If the reason for premature permanent discontinuation of clinical investigation is not an AE, the patient should be withdrawn (withdrawal of consent) and have the EOS visit with all the assessments performed before the medical device discontinuation, whenever possible.

7.2.4 Concomitant medication

The well-being of the patient has the first priority therefore this clinical investigation allows all concomitant medications as long they are stable since over 1 months.

7.2.5 Interactions, reverse reactions and side effect of the medical device:

-Use of the appliance in the vicinity (approx. 1m) of short-wave, microwave or RF appliances can be the cause of interference and must therefore be avoided. (Tested in accordance with EN 60601-1-2.)

Contraindications
- Use of cardiac pacemakers because no clinical data are available
- Hemophilia
- Psoriasis vulgaris, an intact skin surface is essential for the use of P-STIM

7.3 Randomization and stratification:

After the screening visit, patients will be randomized into one of the following treatment groups: group V (Verum electrical vagus stimulation) or group P (placebo).

7.4 Blinding

Patients will receive a dummy of the medical device, which looks like the original. Patient and investigator are blinded. A study nurse controls the list with treatment numbers and treatment groups (placebo or verum).

Unblinding -procedure at the end of the clinical investigation:
At the end of study, codes will be unblinded and data will be analyzed.

7.5 Benefit and risk assessment

A recent safety study summarizes the adverse events of acupuncture. Wheway J et al analyzed 325 incidents during acupuncture treatment. Adverse events reported include retained needles (31%), dizziness (30%), loss of consciousness/unresponsive (19%), falls (4%), Bruising or soreness at needle site (2%), Pneumothorax (1%) and other adverse reactions (12%). The majority (95%) of the incidents were categorised as low or no harm [Wheway J et al, 2012]. On auricular acupuncture in particular we found no safety data. We expect a similar safety profile to body acupuncture.

7.6 Clinical investigation procedures

7.6.1 General rules for clinical investigation procedures

- All clinical investigation measures like blood sampling and measurements (vital parameters, ECG, etc.) have to be documented with date (dd:mm:yyyy).
- In case several clinical investigation procedures are scheduled at the same time point, there is no specific sequence that should be followed.
- The dates of all procedures should be according to the CIP. The time margins mentioned in the clinical investigation flow chart are admissible. If for any reason, a clinical investigation procedure is not performed within scheduled margins a CIP deviation should be noted, and the procedure should be performed as soon as possible or as adequate.
- If it is necessary for organizational reasons, it is admissible to perform procedures which are scheduled for one visit at two different time points. Allowed time margins should thereby not be exceeded.

7.6.2 Screening investigation

BEFORE TREATMENT RANDOMISATION V-1
(Study Day 1)
After signing the informed consent all patients will be screened according to exclusion and inclusion criteria. Patients will be investigated as follows:
-Prior medical history will be assessed.
-ECG (Electrocardiogram) will be performed
-blood pressure
-blood samples will be collected (TNFα, IL6, CRP and NT-proBNP levels will be assessed).
-base line LVEF (not older than 14 days) assessed by transthoracal echocardiography
-6 min walk test
-quality of life assessment with SF 36
- Assessment of NYHA classification (see table 2)

BASE LINE VISIT V0
(Study Day 7)
After randomization to verum or placebo group

-treatment according to randomizations: patients receive dummy or original medical device. Acupuncture will be performed in the concha of the ear. Patients will be instructed how to use device (eg during showering, if the patch removes etc). Device is removed by patient after 4 days.

V1-V4
(Study Day 14, 21, 28, 35)
Patients receive new device, possible adverse events can be assessed, possible complications/questions can be discussed.

Day 21: 6 minutes walk test will be performed again.

End of Study Visit V5
(Study Day 63)
-ECG (Electrocardiogram) will be performed
-blood pressure
-blood samples will be collected (TNFα, IL6, CRP and NT-proBNP levels will be assessed).
-LVEF (not older than 14 days) assessed by transthoracal echocardiography
-6 min walk test
-quality of life assessment with SF 36
-Assessment of NYHA classification

Class	**Patient Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Table 2: New York Heart Association (NYHA) Classification

8. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Adverse events (AEs)/Adverse device effects (ADEs)

8.1.1 Definition of adverse event and adverse device effect

An AE/ADE is any adverse change from the subject's baseline condition, i.e. any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant be the physician that occurs during the course of the, whether or not considered related to the medical device.
Adverse event /ADE include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after treatment with the medical device even though it may have been present prior to the start of the clinical investigation.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to clinical investigation-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs/ADEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the clinical investigation.
- Laboratory test abnormalities must be reported as AEs/ADEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the clinical investigation lead to interruption or permanent discontinuation of medical device.

Adverse events do not include:

- Pre-planned interventions or occurrence of endpoints specified in the CIP are not considered AEs/ADEs, if not defined otherwise.
- Medical or surgical procedure, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE/SADE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Misuse of either medical device or concomitant medication without any signs or symptoms. However, misuse must be mentioned in the Medical Device Inventory/ Treamtment Log.

8.2 Serious adverse events (SAE)/Serious adverse device effects (SADEs)

A Serious Adverse Event (SAE)/Serious adverse device effect is defined as any AE/ADE fulfilling at least one of the following criteria:

- lead s to a death,
- lead s to a serious deterioration in the health of the subject that
  1) resulted in a life-threatening illness or injury,
  2) resulted in a permanent impairment of a body structure or a body function,
  3) required in-patient hospitalization or prolongation of existing hospitalization,
  4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- leads to foetal distress, foetal death or a congenital abnormality or birth defect.
- is an important medical event that may not immediately result in death, be life-threatening, or require hospitalization but may be considered as SAEs/SADEs when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.
- shows the occurance of a malignant tumor (§3 (16) MPG).

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

8.2.1 Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.
An additional overnight stay defines a prolongation of existing hospitalization.
The following is not considered an SAE/SADE and should be reported as an AE/ADE only:

- Treatment on an emergency or out subject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

8.2.2 SAEs /sADE related to study-mandated procedures

Such SAEs /SADEs are defined as SAEs/SADEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of medical device) such as discontinuation of subject's previous treatment or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

8.2.3 Pregnancy

Any pregnancy that occurs during study participation must be reported to the principal investigator/sponsor. **To ensure subject safety, each pregnancy must be reported to the principal investigator/sponsor immediately.** A pregnancy must be followed up to determine outcome

(including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE/ADE or SAE. Spontaneous abortions must be reported as an SAE.
Any SAE occurring in association with a pregnancy,brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the principal investigator/sponsor.
In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the principal investigator/sponsor as described above.
Please enter the address of Investigator/Sponsor!

8.3 Severity of adverse events/adverse device effects

The severity of clinical AEs /ADEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.
If the severity of an AE/ADE worsens during medical device administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Mild
Event may be noticeable to subject; does not influence daily activities; the AE /ADE resolves spontaneously or may require minimal therapeutic intervention;

Moderate
Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE/ADE produces no sequelae.

Severe
Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE/ADE produces sequelae, which require prolonged therapeutic intervention.
A mild, moderate or severe AE/ADE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

8.4 Relationship to medical device

For alls, the investigator will assess the causal relationship between the medical device and the AE/ADE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE/ADE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study product

- Is biologically implausible and does not follow known response pattern to the suspect medical device (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Possible related

- Follows a reasonable temporal sequence form administration of the medical device.
- May follow a known response pattern to the medical device (if response pattern is previously known).
- Could not be reasonable not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable.

Definitely related

- Follows a reasonable temporal sequence form administration of the medical device .
- Follows a known response pattern to the medical device (if response pattern is previously known).
- No other reasonable cause is present.

8.5 Reporting procedures

A special section is designated to adverse events/ADEs in the case report form. The following details must thereby be entered:

- Type of adverse event/ADE
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- Relation to medical device (unrelated, possibly related, definitely related)

Device related adverse events are to be documented in the case report form in accordance with the above mentioned criteria and reported to the Sponsor.

8.5.1 Reporting procedures for SAEs/SADEs

In the event of serious, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the clinical investigator immediately.The following details should be at least available:

- Patient initials and number
- Patient: date of birth, sex, ethical origin
- The suspected medical device
- The adverse event assessed as serious
- Short description of the event and outcome
- Device related or non-device related

The written report is divided into two parts:

- Initial report: Informs about what has happened (AE/ADE assessed as serious), if there is a relationship to the medical device … and which action was set.
- Follow up-Report: informs about the outcome

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

- review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and principal investigator(s)
- review all devices deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor an the principal investigator(s)
- report or ensure the reporting , to the EC and regulatory authorities (AGES) of all serious adverse events and devices.

9. FOLLOW-UP

9.1 Follow-up of clinical investigation participants including follow-up of adverse events

Patients will be followed up 4 weeks after end of clinical trial. If patient finished trial due to an adverse event, he will be followed up closely, namely after 7 days.

9.2 Treatment after end of clinical investigation

Electrical auricular vagus stimulation is accessible to patients after end of clinical investigation.

10.STATISTICAL METHODOLOGY AND ANALYSIS

10.1 Analysis sets

Two different analysis sets are defined:

Intention to treat set
This analysis set includes subjects who were randomized and received at least one dose medical device Main analysis is by the intention-to-treat principle. Here, an outcome value is necessary for each patient, if a patient drops out. Therefore, we will use the interim assessment of walking distance after 2 weeks of treatment, or, if this is unavailable, the baseline measurement (i.e., the patient is counted as a non-responder to treatment) as replacement in such cases.

10.2 Sample size considerations

We assume a clinically relevant difference in the improvement in walking distance of 30 meters comparing the electrically stimulated acupuncture group to the Placebo group. Furthermore, we assume a standard deviation in the improvement o the walking distance of 30 meters (Kirsten 2010).

A sample size of 17 in each group will have 80% power to detect this clinically relevant difference between the groups using a two group t-test with a 0,050 two-sided significance level. Because of the possibility of drop-outs we include 2x20 patients.

10.3 Relevant CIP deviations

All CIP deviations will be listed in the study report.
No deviations from the CIP and of any type will be made without complying with all IRB/EC established procedures in accordance with applicable regulations.

10.4 Statistical analysis plan

The statistical analysis plan will be elaborated by the Prinicipal Investigator together with a statistician.

10.5 Missing, unused and spurious data

Plausibility Checks will be performed regularly, missing data will be treated by the last observation carried forward principle.

10.6 Endpoints analysis

The primary end point (walking distance in 6 minutes) will be analysed by analysis of covariance, taking the baseline value as covariate into account, and the treatment group as factor.

Continuous secondary outcome variables will be analysed by analysis of covariance as described above. Change in NYHA classification will be described by contingency tables, and the percentage of patients with an improvement in NYHA will be compared using a Fisher's exact test.

11.DOCUMENTATION AND DATA MANAGEMENT

11.1 Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

11.1.1 Case report form (CRF)

For each subject enrolled, regardless of medical device initiation, a CRF must be completed and signed by the principal investigator or co-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.
Case report forms are to be completed on an ongoing basis.
CRF entries and corrections will only be performed by study site staff, authorized by the investigator.
In a "Paper-CRF" all forms should be completed using a black pen and must be legible*. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator, co-investigator or study nurse.

The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately.
The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site.

11.2 Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.
The investigator's file will contain the CIP/amendments, IB/Manual for Medical Device, CRFs (eCRF printout), standard operation procedures (SOPs), data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per EUROPENAN Standard of EN ISO 14155 (incl. GCP) and local regulations.
Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.
These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (in Austria 15 years after discontinuing clinical development or after the last marketing approval). If source documents are not durable as long as needed (e.g. ECG printouts) they must be preserved as a copy. No study document should be destroyed without prior written approval from the Department of ……
When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

11.3 Quality Control and Quality Assurance

11.3.1 Periodic Monitoring

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other CIP-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs/SADEs and the recording of the main efficacy, safety, and tolerability endpoints.
To be ISO 14155 compliant at least 3 monitoring visits are scheduled. An initiation visit, one routine visit and a final visit after the last patient had finished the study. The monitor will be working according to SOPs and will provide an ISO 14155-compliant monitoring report after each visit for the

sponsor and the investigator. Depending on the quality of the data, additional monitoring visits will be necessary according to the sponsor's discretion.

11.3.2 Audits and Inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to regulatory authority inspectors. The main purpose of an audit or inspection is to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

12.ETHICAL AND LEGAL ASPECTS

12.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical investigation, the patient must give written consent to participation in the study.
During the instruction the patients are to be made aware of the fact that they can with-draw their consent – without giving reasons – at any time without their further medical care being influenced in any way.
In addition to the comprehensive instructions given to the patients by the investigator, the patients also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.
The patients must agree to the possibility of study-related data being passed on to relevant authorities.
The patients must be informed in detail of their obligations in relation to the proband insurance in order not to jeopardize insurance cover.

12.2 Acknowledgement / approval of the clinical investigation

The investigator *(or a designated CRO*) will submit this CIP and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the clinical investigation, and should be documented in a dated letter to the investigator.
Serious Adverse Events /Serious Adverse Device Effects have to be reported to the ethics committee and to the Austrian Agency for health and Food Safety (AGES).
Adverse events / Adverse device effects- whether serious and/or unexpected, and possibly endangering the safety of the study participants are likewise to be reported to the ethics committee.
The clinical investigation shall be performed in full compliance with the valid legal regulations according to the Medical Device Law (MPG Medizinproduktegesetz as actual amendet) of the Republic of Austria and the ISO 14155 (as actual amended)
The study must be notified to the Austrian Agency for Health and Food Safety (AGES) and Ethics Committee.

12.2.1 Changes in the Conduct of the Clinical Investigation Plan

Amendments of the clinical investigation plan
Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Termination of the clinical investigation
If the sponsor or the investigator decides to terminate the clinical investigation before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or designated CRO will notify the relevant regulatory authorities and EC. Documentation will be filed in the Trial Master (Clinical Investigation) clinical investigationand Investigator Files.

12.3 Insurance

During their participation in the clinical investigation the patients will be insured as defined by legal requirements. The principal investigator of the clinical investigation will receive a copy of the insurance conditions of the 'patients insurance'. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the clinical investigation, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of clinical investigation-related injuries will comply with the applicable regulations.
Details on the existing patients insurance are given in the patient information sheet.
Wird nachgereicht!

12.4 Confidentiality

.
The information contained in this document, especially unpublished data, is the property of the Dept. of Special Anaesthesia and Pain Therapy, Medical University of Vienna. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Dept. of Special Anaesthesia and Pain Therapy, Medical University Vienna, except to the extent necessary to obtain informed consent from those persons to whom the medical device may be treated with.

12.5 Ethics and legal requirements

12.5.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008).

12.5.2 Good Clinical Practice (EN ISO 14155)

ISO 14155 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety and performance of medical devices for regulatory purposes .

It specifies general requirements intended to:

- protect the rights, safety and well-being of human subjects,
- ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other
- bodies involved in the conformity assessment of medical devices.

The principal investigator of the clinical investigation shall guarantee that only appropriately trained personnel will be involved in this. All clinical investigations must follow the EUROPENAN Standard of EN ISO 14155 and, if applicable, the Code of Federal Regulations (USA). In other countries in which EN ISO Guidelines exist, the investigators will strictly ensure adherence to the stated provisions. Therefore this study follows the EN ISO Guidelines embedded in the Austrian medical device act.

13.APPENDICES

14.REFERENCES

1. Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat 2002;15:35-7.
2. Schwartz PJ, De Ferrari GM. Sympathetic-parasympathetic interaction in health and disease: abnormalities and relevance in heart failure. Heart Fail Rev;16:101-7.
3. Mortara A, La Rovere MT, Pinna GD, et al. Depressed arterial baroreflex sensitivity and not reduced heart rate variability identifies patients with chronic heart failure and nonsustained ventricular tachycardia: the effect of high ventricular filling pressure. Am Heart J 1997;134:879-88.
4. La Rovere MT, Pinna GD, Maestri R, et al. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. J Am Coll Cardiol 2009;53:193-9.
5. Aukrust P, Ueland T, Lien E, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1999;83:376-82.
6. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 1996;27:1201-6.
7. Aukrust P, Ueland T, Muller F, et al. Elevated circulating levels of C-C chemokines in patients with congestive heart failure. Circulation 1998;97:1136-43.
8. Damas JK, Gullestad L, Ueland T, et al. CXC-chemokines, a new group of cytokines in congestive heart failure--possible role of platelets and monocytes. Cardiovasc Res 2000;45:428-36.
9. Kapadia SR. Cytokines and heart failure. Cardiol Rev 1999;7:196-206.
10. Pomerantz BJ, Reznikov LL, Harken AH, Dinarello CA. Inhibition of caspase 1 reduces human myocardial ischemic dysfunction via inhibition of IL-18 and IL-1beta. Proc Natl Acad Sci U S A 2001;98:2871-6.
11. Gullestad L, Ueland T, Vinge LE, Finsen A, Yndestad A, Aukrust P. Inflammatory cytokines in heart failure: mediators and markers. Cardiology;122:23-35.
12. Lecour S, James RW. When are pro-inflammatory cytokines SAFE in heart failure? Eur Heart J;32:680-5.
13. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 2002;91:988-98.
14. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009;55:53-60.
15. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 2005;112:1428-34.
16. Coats AJ. The "muscle hypothesis" of chronic heart failure. J Mol Cell Cardiol 1996;28:2255-62.
17. Kristen AV, Schuhmacher B, Strych K, et al. Acupuncture improves exercise tolerance of patients with heart failure: a placebo-controlled pilot study. Heart;96:1396-400.
18. Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. Eur J Heart Fail 2008;10:884-91.
19. Schneider A, Streitberger K, Joos S. Acupuncture treatment in gastrointestinal diseases: a systematic review. World J Gastroenterol 2007;13:3417-24.
20. Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, Klein J. Anti-inflammatory actions of acupuncture. Mediators Inflamm 2003;12:59-69.

21. La Marca R, Nedeljkovic M, Yuan L, Maercker A, Elhert U. Effects of auricular electrical stimulation on vagal activity in healthy men: evidence from a three-armed randomized trial. Clin Sci (Lond);118:537-46.